REMARKS

Claims 1-49, 51, 53, 54, 64, 69, 71, and 79-83 have been cancelled without prejudice or disclaimer. Accordingly, claims 50, 52, 55-63, 65-68, 70, 72-78, and 84 are pending in the application.

Rejection of claims under 35 U.S.C. §102 for anticipation

Claims 50, 55-63, 65-68, 70, and 84 are rejected under 35 U.S.C. §102(e) as being anticipated by Kaplan et al. (US Patent 5,941,868, hereinafter "Kaplan").

Claims 50, 55-63, 65-68, 70, and 84 are rejected under 35 U.S.C. §102(e) as being anticipated by Ferrara et al. (US Patent 5,332,671, hereinafter "Ferrara").

For brevity, the rejections will be considered together.

Claim 50 is the only independent claim in the rejection with all of the remaining claims dependent thereon either directly or indirectly. Claim 50 directed to a "method for inducing new blood vessels in a mammal having chronic or acute ischemia… [that] comprises administering to the mammal an effective amount of a vascular endothelial growth factor (VEGF) and a granulocyte-macrophage colony stimulating factor (GM-CSF), or an effective fragment thereof." Therefore the claim requires administration of both a VEGF and GM-CSF.

The Office Action at the bottom of page 7 states, "However, neither Kaplan et al. nor Ferrara et al teach the use of both VEGF and GM-CSF in a method for inducing new blood vessels in a mammal having chronic or acute ischemia."

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). By the admission of the Examiner, neither Kaplan nor Ferrara teach each and every element of the claim as is required for a proper anticipation rejection. Withdrawal of the rejection is respectfully requested.

Rejection of claims under 35 U.S.C. §103 for obviousness

Claims 50, 52, 55-63, 65-68, 70, 72-78, and 84 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over either Kaplan or Ferrara in view of Bussolino et al. (hereinafter Bussolino).

The Office Action states that Kaplan teaches methods for promoting angiogenesis in tissue surrounding a body lumen with exemplary angiogenic factors including VEGF, bFGF, aFGF, EGF, PDGF, and fragments and combinations thereof. The Office Action also states that Ferrara teaches a method for treating trauma affecting the vascular endothelium by administering VEGF optionally with other novel or conventional therapies including treatment with growth factors.

The Office Action also states that Bussolino demonstrates that G-CSF and GM-CSF are capable of inducing endothelial cells to proliferate and migrate in vitro, repair wounded monolayers, and act synergistically with bFGF in a corneal model of angiogenesis. From these results, the Office Action asserts that it would have been obvious for an ordinary skilled artisan to modify either Kaplan or Ferrara by using G-CSF or GM-CSF in combination with VEGF to promote angiogenesis in the claimed methods.

Applicant respectfully disagrees.

Section 2143.01(III) of the MPEP states:

> The mere fact that references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art. *KSR International Co. v. Teleflex Inc.*, 550 U.S. ___, ___, 82 USPQ2d 1385, 1396 (2007)("If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability. For the same reason, if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill.").

The equivocal statements regarding the meaning of the data in the Bussolino reference would not suggest reliance on the reference regarding the activity of G-CSF or GM-CSF with FGF. Specifically, in the right hand column of page 994, Bussolino states:

> The cooperative angiogenic activity of G-CSF and bFGF was evident in terms of response intensity (number of capillaries, number of positive implants, time to reach the pellets). ***This initial observation needs to be extended.*** However, the cooperative effect of G-CSF and bFGF in inducing in vivo angiogenesis was somewhat ***surprising*** and intriguing. In fact, in vitro, in spite efforts involving different experimental designs only one of which is shown here (see Results), we have found ***no indication of a synergistic action*** of these two cytokines on HUVEC proliferation and migration. ***At best, an additive effect was observed.*** In vivo angiogenesis occurs as the endpoint of complex interactions between many events involving remodeling of the extracellular matrix and the release of several "factors" (12, 50). This apparent ***paradox*** of a combination of cytokines acting directly on endothelial cells, showing a cooperative effect in vivo, but not in vitro, adds to the list of factors or conditions for which in vitro modulation of proliferation and migration is not necessarily predictive of in vivo effects on angiogenesis. (emphasis added)

Brussolino teaches that the observations were ***"surprising"***. In other words, Brussolino, one of skill in the art, did not find his results predictable. The data resulted in a ***"paradox"*** rather than an understanding. That is more experiments need to be done as conclusions cannot be drawn from the results presented in the reference. The reference provides an invitation to further experimentation rather than firm conclusions.

Again, per the MPEP (Section 2141.02 (VI)):

> A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984) (Claims were directed to a process of producing a porous article by expanding shaped, unsintered, highly crystalline

> poly(tetrafluoroethylene) (PTFE) by stretching said PTFE at a 10% per second rate to more than five times the original length. The prior art teachings with regard to unsintered PTFE indicated the material does not respond to conventional plastics processing, and the material should be stretched slowly. A reference teaching rapid stretching of conventional plastic polypropylene with reduced crystallinity combined with a reference teaching stretching unsintered PTFE would not suggest rapid stretching of highly crystalline PTFE, in light of the disclosures in the art that teach away from the invention, i.e., that the conventional polypropylene should have reduced crystallinity before stretching, and that PTFE should be stretched slowly.).

When the Bussolino reference is taken as a whole, per the author, no conclusion can be reached other than more experiments must be done. Bussolino does not provide a reasonable expectation as to how further experiments using his combination of growth factors and cytokines will result, never mind how other combinations will result. Such an equivocal reference cannot provide a motivation to modify another reference. Withdrawal of the rejection is respectfully requested.

Claims 50, 52, 55-63, 65-68, 70, 72-78, and 84 are rejected uner 35 U.S.C. § 103(a) as allegedly being unpatentable over Kaplan in view of Hammond et al. (US Patent 5,880,090, hereinafter Hammond) and Asahara et al. (Science, 1997, hereinafter Asahara).

The Office Action alleges that Kaplan taught methods for promoting angiogenesis in tissue surrounding a body lumen in a region of ischemic tissue by delivering an angiogenic factor to a target site. Exemplary angiogenic factors including VEGF, bFGF, aFGF, EGF, PDGF, and fragments thereof. However, the Office Action states that Kaplan did not teach the combination of both VEGF and GM-CSF. The Office Action further alleges that Hammond taught administration of an agent including stem cell factor, GM-CSF, and G-CSF into a graft recipient to mobilize endothelial progenitor cells into the bloodstream. Hammond is also alleged to have taught that more than one endothelial-promoting agent including FGF, VEGF, and angiopoietin may be administered concomitantly. Hammond is also alleged to have noted that Asahara had shown that CD34+ endothelial cell populations are capable of differentiating into endothelial-

like cells and may participate in the repair of ischemic tissue.

The Office Action states that it would have been obvious for an ordinary skilled artisan to modify the method of Kaplan by administering into a mammal having ischemia using an agent such as SCF, Gm-CSF, and G-CSF.

The Office Action also alleges that the Rule 131 Declaration submitted by the Applicant is insufficient to antedate the Hammond reference. The Office Action states that the Declaration is insufficient and that it does not demonstrate conception of the invention prior to September 19, 1997. Applicant respectfully disagrees.

The Declaration provides data from the specific combination of VEGF and GM-CSF as claimed. At point 8 and in Exhibit 2, Applicant demonstrates that the combination of VEGF and GM-CSF are effective in promoting angiogenesis in an accepted *in vivo* model. The corneal angiogenesis model allows for the study of the effects of potentially angiogenic factors in a tissue that is avascular that can be observed over time without disrupting the tissue. At the same time that the inventors were performing angiogenic assays using a combination of VEGF and GM-CSF in cornea, they were also performing angiogenesis assays in ischemic animal models using GM-CSF. Moreover, they were studying the mechanism of action of GM-CSF on endothelial progenitor cells which provided an understanding of the role of GM-CSF in neovascularization that allowed them to better correlate results from multiple neovascularization models.

Conception does not require an actual reduction to practice. Therefore, although the Declaration does not include data demonstrating the use of VEGF and GC-CSF in an ischemic limb model, it does not preclude conception of the invention prior to the effective date of Hammond. The Declaration teaches that the change in EPC kinetics due to treatment with GM-CSF results in increased neovascularization. As a change in kinetics would result in a systemic effect, demonstration of an effect on neovascularization in one tissue (e.g., cornea) would result in the understanding that the same effect would be seen in neovascularization in all tissues. Specifically, page 2 of Exhibit 2 states:

> These results indicates GMCSF exerts potent stimuli on EPC kinetics and such a cytokine-induced EPC mobilization can enhance neovascularization in

severe ischemia condition and de novo vascularization in avascular area.

Therefore, the Declaration demonstrates that the inventors had conceived that the effects observed in an ischemic model, as claimed, would be predictive of results that would be obtained in an avascular area, e.g., cornea. Similarly, the inventors understood that the data obtained in the corneal model, discussed at point 8 of the Declaration, would be predictive of results that would be observed in an ischemic model.

The data in the specification combined with the conclusions in the manuscript demonstrate full conception of the invention as claimed. As the invention was conceived prior to the date of the Hammond reference, it is not available for the rejection of the claims for obviousness. As the combination of the Kaplan and Asahara references is insufficient to make the claimed invention obvious, the rejection is overcome. Withdrawal of the rejection is respectfully requested.

CONCLUSION

Applicant submits that the claims are now in proper form for allowance. However, if the Examiner believes that there are outstanding issues in the case, the Examiner is encouraged to contact the Agent for Applicant listed below by telephone to discuss the matter.

Applicant believes no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. **04-1105.**

Dated: May 23, 2008

Respectfully submitted,

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